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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,441	04/15/2004	Patrick M. Hughes	17686 (OCU)	1056

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EXAMINER	
MAASHO, KERIMA K	
ART UNIT	PAPER NUMBER
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,441	HUGHES ET AL.	
	Examiner	Art Unit	
	Kerima Maasho	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/2/06, 9/9/05, 9/9/05, 6/30/04.

DETAILED ACTION

Claim rejections-35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 16, 18, 21-23, 26, 28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially identical" in claims 16, 18, 21-23, 26, 28, and 30 is a relative term that renders the claim indefinite. The claims that are dependent on these indefinite claims do not resolve the indefiniteness of the term "substantially identical", therefore Claims 17, 19, and 20; claims 27, 28, and 29; and claims 31, 32 and 33 are indefinite insofar as they depend from claims 16, 26 and 30 respectively. The term "substantially identical" is not defined by the claims, and the specification does not provide a standard for ascertaining the requisite degree, therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim rejections-35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Donovan U.S. patent 6,506,399 B2 (made of record on the IDS filed 6/30/04). Claims 1-25 are drawn to a biodegradable neurotoxin implant. Donovan relates to an implantable botulinum toxin delivery system using a biodegradable polymer as a carrier for the neurotoxin whereby suitable pH conditions to form a complex of neurotoxin are shown to include pH values between 5.0 and 6.9 (column 23, lines 54-58). Donovan further teaches that the ratio of different monomers such as lactide and glycolide comprising a polymer; the use of L-isomer of a monomer and the molecular weight of the polymer affect the properties of the polymer and control the rate of polymer degradation (column 25, lines 16-22). Donovan further teaches that it is possible to add an acidic or a basic excipient to the polymer solution used to form the microsphere to alter the polymer erosion rate (column 25, lines 34-37). The acidity-regulating component of the current application comprises monomers from which a biodegradable polymer is derived and the implant further comprises salts of the monomer. While the reference of Donovan *et al.* does not specifically teach the pH regulation caused by the monomer the property is inherent to the monomers of the lactide and glycolide used. Therefore, Donovan meets each and every limitation of claims 1-25.

2. Claims 1, 16-23, 25-33 are rejected under 35 U.S.C. 102 as being anticipated by Donovan, U.S. patent No. 6,312,708. Claims 16-23, 25-33 in the present invention contain an acidity-regulating component including at least one of monomers and oligomers from which a biodegradable polymer is derived. Donovan's invention encompasses an implantable botulinum toxin delivery system using polymeric microspheres. Donovan teaches that changing polymer properties that influence the rate of hydration of the polymer can control the rate of polymer implant degradation. These properties include, for instance, the ratio of different monomers, such as lactide and glycolide, comprising a polymer; the use of the L-isomer of a monomer instead of a racemic mixture; and the molecular weight of the polymer. These properties can affect hydrophilicity and crystallinity, which control the rate of hydration of the polymer. Hydrophilic excipients such as salts, carbohydrates and surfactants can also be incorporated to increase hydration and which can alter the rate of erosion of the polymer (column 25, lines 27-38). This reference points out the presence of different monomers comprising a polymer in a biodegradable implant that reads on the monomers of the current invention whose claimed acidity regulating component also includes monomers from which biodegradable polymer is derived.

Donovan teaches that basic salts from the polymer implant can be used to regulate or neutralize the polymer microclimate pH to levels necessary to retain the structure and biological activity of encapsulated acid-labile proteins. The source of the acidity-regulating component is an inherent property of the

polymers used in the biodegradable implant of the present application, therefore, Donovan meets the limitations of the acidity-regulating component of the present invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 26-30 are rejected under 35 U.S.C. 103 as being obvious over Donovan U.S. patent No. 6,506,399 (made of record on the IDS filed 6/30/04) in view of Agarwal U.S. patent No. 5,741,329. Claims 1 and 26-30 refer to the acidity-regulating component whereby a method of controlling the pH in the vicinity of biodegradable implants was described. It is known that pure botulinum toxin is labile and that botulinum toxin type A complex are extremely susceptible to denaturation due to heat and alkaline conditions. Donovan teaches that denaturation of the encapsulated neurotoxin, botulinum toxin type A, in the body at 37 degrees C. for a prolonged period of time can be reduced among other things with lyophilization from an acidic solution using a specific polymer matrix composition. Therefore the alkaline lability of the neurotoxin is an obvious motivation for a pH-regulating component. Moreover, Agarwal *et al.* discloses a method of controlling the pH in the vicinity of biodegradable implants. Agarwal *et al.* further teaches that a pH regulating substance included with the biodegradable polymer hinders shifts in pH that typically occur as the polymer breaks down (column 2-3, lines 67-70). The pH controlled implantable device comprises the biodegradable polymer polylactic acid, polyglycolic acid, polycaprolactone, copolymers thereof, or mixtures thereof (column 4, lines 48-51). The pH controlling substance of the device may comprise an alkaline substance, an acidic substance or a buffering agent, depending upon the acidic or alkaline nature of the polymeric breakdown products of the particular biodegradable polymer employed (column 5, lines 4-8). These features are applicable in polymer-based orthopedic implantable devices as well as implants

employed for the delivery of pharmacologically active substances such as a neurotoxin. Therefore the source of the acidity-regulating component is an inherent property of the polymers.

The teachings of Donovan and Agarwal offer a motivation as well as reveal the inherent properties of the monomers from which the biodegradable polymer is derived.

Claims 1, 11-13 are rejected under 35 U.S.C. 103 as being obvious over Donovan U.S. patent No. 6,506,399 (made of record on the IDS filed 6/30/04) in view of Gurny *et al.* U.S. patent No. 6,440,460. Claims 1, and 11-13 refer to the acidity-regulating component to be effective in maintaining a pH of the implant to a value of less than 7, within a range of about 3 to 7.

Donovan teaches that a pH above about pH 7 can cause the stabilizing nontoxin proteins to dissociate from the botulinum toxin resulting in gradual loss of toxicity, during toxin complex mix in vitro. The preferred pH range for the casting or other solution in which the botulinum toxin is to be mixed is between about 5-6 (column 28, lines 62-67). Likewise, a pH of about 5.5 or lower is required in vivo for the toxin to embed itself in the endosomal membrane of a target cell. Once the toxin enters the cells through receptor-mediated endocytosis, an endosome containing the toxin is formed. The toxin then escapes into the cytoplasm of the cell where it encounters a low pH. This leads to conformational change of the toxin to occur which results in exposure of hydrophobic residues in the toxin to permit the toxin to embed itself in the endosomal membrane of a target cell (column 5, lines 17-

27). Donovan's teaching gives the basis for using an acidic environment for the stability of the botulinum toxin.

Gurny *et al.* teaches that the decomposition of ortho ester polymer results in carboxylic acid release. The amount liberated increases upon progressive hydrolysis of the ortho ester polymer. This causes a decrease of the pH-level in-vitro from values of about 6.5 to 4.5 to even lower values in 1-5 days depending on the molecular weight of the polymer (column 1, lines 53-67). A buffered system in the physiologically acceptable range could be maintained by using acid salts such as glycolate and lactate (column 6, lines 60-67). Gurny et al. teaches the possibility for modifying the pH environment depending on the molecular weight of the polymer to desired range by use of the inherent acidic property of the polymers and salts of acids.

Donovan teaches specifically about a biodegradable botulinum toxin implant and the importance of maintaining acidic environment for the controlled release of botulinum toxin in vivo. Gurny et al. teaches generally about pharmaceutical compositions containing buffered polymers of biodegradable implant. Together the teachings of Donovan and Gurny give a basis for claims 1, 11-13, by offering a motivation as well as revealing the inherent properties of the monomers from which the biodegradable polymer is derived. Basic salts of the polymer can be used to regulate or neutralize the polymer microclimate pH to levels necessary to retain the structure and biological activity of encapsulated labile proteins. Moreover these teachings are within the range of the claimed pH of the present application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kerima Maasho whose telephone number is 571-270-3055. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MARY E. MOSHER, PH.D.
PRIMARY EXAMINER

2-2-07